

REMARKS

Amendments

The claims are amended to be in accordance with conventional US practice, to correct errors in spelling and punctuation, and to delete unnecessary language. These amendments do not narrow the scope of the claims.

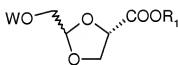
Claim Objections

Claims 1 and 12 are amended to recite, "subjecting a compound." Withdrawal of the objection is respectfully requested.

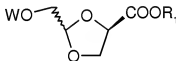
Rejection under 35 USC 103(a) in view of Cimpoia et al., Janes et al., and Ferrero et al.

Claims 1-24 are rejected as allegedly being obvious in view of Cimpoia et al. (WO 00/47759), the article by Janes et al., and the article by Ferrero et al. This rejection is traversed.

Cimpoia et al. (WO '759) disclose a process for separating β and α anomers from an anomeric mixture. This mixture is represented by either formula A or formula B:



(A)



(B)

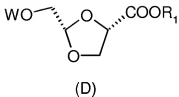
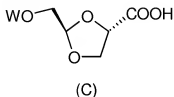
In these formulas, W is benzyl or benzoyl, and R₁ is H, C₁₋₆ alkyl or C₆₋₁₅ aryl. The anomeric mixture is hydrolyzed with an enzyme selected from cholesterol esterase, ESL-001-02, horse liver esterase, bovine pancreatic protease, α -chymotrypsin, protease from *Streptomyces caespitosus*, subtilisin from *Bacillus licheniformis*, protease from *Aspergillus oryzae*, proteinase from *Bacillus licheniformis*, protease from *Streptomyces griseus*, acylase from *Aspergillus mellus*, proteinase from *Bacillus subtilis*, ESL-001-05, pronase protease from *Streptomyces griseus*, lipase from *Rhizopus arrhizus*, lipoprotein lipase from *Pseudomonas* species type B, lipase from *Pseudomonas cepacia*, and bacterial proteinase. See page 7, line 6 - page 8, line 7.

In this process, the hydrolyzing step stereoselectively hydrolyzes the α -anomer of the

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mixture of either formula A or formula B. This results in a mixture of the hydrolyzed α -anomer and the unhydrolyzed β -anomer, and the hydrolyzed α -anomer is then separated from the β -anomer.

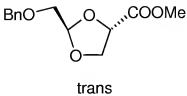
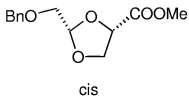
Thus, for example, if an anomeric mixture of formula A is treated in accordance with the disclosed process, the result is the production of a mixture of the compound of formula C and the compound of formula D:



See page 14, line 20 – page 15, line 17. As can be seen, the hydrolysis is performed on the COOR_1 group attached to the C4 position of the sugar ring (dioxolane ring).

As is acknowledged in the rejection Cimpoia et al. do not disclose the use of Pig Liver Esterase or Porcine Pancreatic Lipase (compare applicants' claim 1), nor does Cimpoia et al. do not disclose the use of Candida Antarctica "A" lipase, Candida Antarctica "B" lipase, Candida Lypolitica Lipase, or Rhizomucor Miehei Lipase (compare applicants' claim 12).

Janes et al. disclose the use of α -chymotrypsin and bovine pancreatic protease for separating *cis* and *trans* diastereomers of 2(R,S)-benzoyloxymethyl-1,3-dioxolane-4(S)-carboxylic acid methyl ester, wherein the hydrolysis occurs at the carboxyl group. Janes et al. disclose that they discovered these two selective hydrolase enzymes "by screening a library of 91 commercial hydrolases." See the abstract. The *cis* and *trans* diastereomers of 2(R,S)-benzoyloxymethyl-1,3-dioxolane-4(S)-carboxylic acid methyl ester are shown below:



In the initial screening test, the diastereoselectivity of the enzymes was estimated by

determining their rates of hydrolysis with respect to the individual pure diastereomers, i.e., the *cis* 2(S)-benzoyloxymethyl-1,3-dioxolane-4(S)-carboxylic acid methyl ester and the *trans* 2(R)-benzoyloxymethyl-1,3-dioxolane-4(S)-carboxylic acid methyl ester. See Table 1. Based on these initial results, Janes et al. selected 6 enzymes for further study, i.e., α -chymotrypsin, bovine pancreatic protease, subtilisin from *Bacillus licheniformis*, bovine cholesterol esterase, protease from *Streptomyces caespitosus*, and horse liver esterase. Diversa clonenzyme ESL-001-02 showed moderate estimated diastereoselectivity, but was not selected for further study because it is expensive. See page 9021, right column. It is noted that all seven of these enzymes are among the group of enzymes disclosed by Cimpoia et al. Thus, the disclosure of Janes et al. adds nothing to the disclosure of Cimpoia et al.

In fact, the disclosure of Janes et al. actually teaches away from applicants' claimed invention. As noted above, of the 91 enzymes screened, Janes et al. selected only 6 enzymes as warranting further study. Included among the tested enzymes that exhibit insufficient estimated diastereoselectivity are pig liver esterase, *Candida Antarctica* "A" lipase, *Candida lypolitica* lipase, and *Mucor miehei* lipase. The estimated diastereoselectivity is determined as the ratio of *cis*/*trans* or *trans*/*cis* activity. For the α -chymotrypsin, bovine pancreatic protease, subtilisin from *Bacillus licheniformis*, bovine cholesterol esterase, protease from *Streptomyces caespitosus*, and horse liver esterase, the ratio was greater than 8. But, for pig liver esterase, *Candida Antarctica* "A" lipase, *Candida lypolitica* lipase, and *Mucor miehei* lipase, the ratio was 2.09 or lower [pig liver esterase 1.41 (*trans*) and 2.09 (*trans*); *Candida Antarctica* "A" lipase 1.60 (*cis*); *Candida lypolitica* lipase 1.4 (*trans*); and *Mucor miehei* lipase 1.36 (*cis*)]. Such low estimated diastereoselectivity suggests away from using these enzymes to separate a diastereomeric mixture.

In the article by Ferrero et al., Table 1 is said to list enzymes that are commonly used in biocatalytic processes and which are mentioned in the review article. Included in this list are pig liver esterase (PLE), porcine liver esterase (PPL), and *Candida Antarctica* "B" lipase (CAL).

The reaction procedures using PLE and PPL are illustrated in schemes 12 and 13 (pages 593-594), respectively. In these reactions, the enzymes induce hydrolysis of the RO-CH₂- group attached to the C2 position of the sugar ring, not hydrolysis of the group attached to the C4 position of the sugar ring. See also the use of PLE in scheme 15 (page 595).

In schemes 20-25 (pages 598-604), CAL is used to induce acylation or alkoxycarbonylation of the group at the C2 position of the sugar, not hydrolysis of the group attached to the C4 position of the sugar. Scheme 22 also shows the use of CAL to induce hydrolysis of an acyl group at the C2 position of the sugar. Thus, the disclosure of Ferrero et al. provides no suggestion of using liver esterase (PLE), porcine liver esterase (PPL), or Candida Antarctica "B" lipase (CAL) in a reaction for diastereoselectively hydrolyzing the group attached to the C4 position of a dioxolane compound such as in the case of the mixtures of Formulas A and B of Cimpoa et al.

In view of the above remarks, one of ordinary skill in the art, taking the combined disclosures of Cimpoa et al., Janes et al., and Ferrero et al., would not be lead to modify the process of Cimpoa et al. in such a manner as to arrive at a process in accordance with applicants' claimed invention. Thus, it is respectfully submitted that Cimpoa et al., taken alone or in combination Janes et al. and/or Ferrero et al., fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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